The Levels of Serum B12, Folic Acid and Homocysteine in the Thromboembolic Diseases

Tromboembolik Hastalıklarda Serum B12, Folik Asit ve Homosistein Düzeyi

Homocysteine in Thromboemboli

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Özet

Amaç: Bu çalışmanın amacı acil serviste tromboembolik hastalık (derin ven trombozu, pulmoner emboli, akut koroner sendrom, serebrovasküler hastalık gibi) tanısı konan hastalarda başvuru sırasındaki serum B12, folik asit ve homosistein düzeylerini incelemek, tanılarına göre grupları sağlıklı bireyler ile ve birbiri ile karşılaştırmaktır. Gereç ve Yöntem: Çalışmaya Mart 2009- Mayıs 2009 tarihleri arasında acil serviste Akut Miyokart İnfarktüsü, Akut Pulmoner Emboli, Derin Ven Trombozu, İskemik Serebrovasküler Hastalık, Akut Mezenter Emboli, Periferik Arter Embolisi tanıları konmuş 100 hasta ve kontrol grubuna 110 sağlıklı gönüllü alındı. Hastaların başvuruda alınan serum örneklerinden vitamin B12, folik asit ve homosistein düzeyleri çalışıldı. Grupları arasındaki karşılaştırma Mann-Whitney U testi ile yapıldı. Hasta grubunda tanılarına göre karşılaştırmada Kruskal-Wallis varyans analizi kullanıldı. p≤ 0.05 değerleri anlamlı kabul edildi. Bulgular: Ortalama serum homosistein ve plazma vitamin B12 düzeyleri hasta grubunda kontrol grubundan anlamlı yüksek bulundu (sırası ile p=0.002, 0.000). Ortalama serum vitamin B12 düzeyleri tanılarına göre hasta gruplarından Serebro vasküler olay ve Akut Miyokard İnfarktüsü gruplarında kontrol grubundan anlamlı düşük bulundu (p<0.05). Pulmoner emboli ve Akut Miyokard İnfarktüsü gruplarında serum folik asit düzeyi kontrol grubundan anlamlı düşüktü (p<0.05). Plazma homosistein düzeyleri tanılarına göre tüm hasta gruplarında kontrol grubundan anlamlı yüksek bulundu (p<0.05). Tartışma: Tromboembolik hastalıklardan ST yükselmeli Miyokart infarktüs, ST yükselmesiz Miyokart infarktüs, Pulmoner emboli ve Serebro vasküler olayda akut dönemde kabulde serum vitamin B12 ve folik asit düzeyleri diğer tromboembolik hastalıklardakinden düşüktür. Bütün tromboembolik hasta gruplarında akut dönemde plazma homosistein düzeyleri yüksek olup; Pulmoner emboli, ST yükselmeli Miyokart infarktüs ve ST yükselmesiz Miyokart infarktüs, gruplarında en yüksek değerdedir.

Anahtar Kelimeler

Vitamin B12; Folik Asit; Homosistein

Abstract

Aim: The aim of this study was to examine the levels of serum B12, folic acid, and homocysteine at admission in the cases established at the emergency department with thrombo-embolic diseases and to compare them with healthy subjects and also compare the diagnosis groups with each other. Material and Method: This study included 100 subjects diagnosed at the emergency department between March 2009-May 2009 with acute myocardial infarction, acute pulmonary embolism, deep vein thrombosis, ischemic cerebrovascular disease, acute mesenteric embolism, peripheral artery embolism and 110 healthy voluntary subjects were included in the control group. Vitamin B12, folic acid, and homocysteine levels were examined in blood samples obtained at admission. Mann-Whitney U test was used to compare the patient and control group. Kruskal-Wallis variance analysis was used to compare the patient group, according to diagnosis. p≤ 0.05 was considered as significant. Results: Mean serum homocysteine and plasma vitamin B12 levels were significantly higher in the patient group than control group (p=0.002, 0.000 respectively). Mean serum B12 values of acute myocardial infarction and Ischemic Cerebrovascular Disease groups in the patient group were significantly lower than those of the control group (p<0.05). Serum folic acid values of peripheral artery embolism and acute myocardial infarction groups were considerably lower than the control group (p<0.05). Plasma homocysteine levels were significantly higher in all patient groups according to their diagnosis than the control group (p<0.05). Discussion: Serum vitamin B12 and folic acid levels in the acute period of thromboembolic diseases of ST-elevation myocardial infarction, non-ST elevation myocardial infarction, pulmonary embolism, and ischemic cerebrovascular disease are lower than those of other thromboembolic diseases. Plasma homocysteine levels are high during the acute period of all thromboembolic diseases; they are at the highest levels in acute pulmonary embolism, ST-elevation myocardial infarction, and non-ST elevation myocardial infarction which have high morbidity and mortality rates when compared with the other thromboembolic diseases.

Keywords

Vitamine B12; Folic Acid; Homocysteine

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Introduction

Atherosclerosis, diabetes mellitus, vasculitis, grafts and prosthetic valves, conditions leading to stasis, hyperviscosity, myeloproliferative diseases, and thrombotic abnormalities such as thrombocytosis, coagulation disorders, and disorders of the fibrinolytic system are predisposing factors for thromboembolic diseases [1, 2].

Homocysteine (hcy) is not found in the diet, but it is an intermediate metabolite of methionine metabolism [3]. Congenital abnormalities of the hcy-methionine cycle lead to hyperhomocysteinemia (hhcy). Lately, attention has been directed toward hyperhomocysteinemia due to acquired pathologies such as nutrient deficiency and toxicity. The relationship between coronary heart diseases (CAD), vascular diseases, and hyc has been known for a long time [4-6]. The effect of Hhyc on atherogenic events has been explained using two pathophysiological mechanisms. One is based on thrombus formation caused by a distortion of endothelial function due to thrombocyte activation and endothelial injury [7]. Hcy necessitates vitamin B12 and folic acid. The hcy level can be affected by genetic enzyme variation or dietary vitamin intake [4, 5, 8, 9]. Even though hcy has been determined as a risk factor for venous thrombosis, its effect on ischemic cerebrovascular diseases or other thromboembolic conditions has not yet been defined. There are some studies showing a strong relationship between hcy level and cerebral infarction [10].

In this study, we aimed to compare the serum levels of vitamin B12, folic acid, and homocysteine of patients in the emergency unit who were diagnosed with thromboembolic diseases (pulmonary embolism, peripheral artery embolism, and acute myocardial infarction) with each other and with a control group.

Method and Material

The study was conducted in the Emergency Clinic of a University Hospital between March 2009 and May 2009. Approval from the ethics committee of the faculty of medicine was obtained. One hundred patients diagnosed with ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), pulmonary embolism (PE), ischemic cerebrovascular event (ICE), peripheral artery embolism (PAE) and deep venous thrombosis (DVT) in the emergency unit were included in the study. Patients with a previous history of stroke, using vitamin B12 and/ or folic acid replacement, taking anti-metabolic medications, having a history of dyslipidemia, migraine, chronic renal failure, chronic liver failure, diabetes, malignancy, hematological disease, and valvular heart disease were not included in the study. 110 healthy volunteers were included in the control group. Every patient was given information about the study and informed consents were obtained. Venous blood samples from the diagnosed patients and control patients were put into gel Vacutainer tubes for vitamin B12 and folic acid and into EDTA tubes for homocysteine level determination. Blood samples were centrifuged for 10 minutes at 3500 rpm. Plasma samples for homocysteine and serum samples for vitamin B12 and folic acid were put into eppendorf tubes. The samples were conserved at -20°C until biochemical evaluation. All samples for homocysteine were analyzed by an Immulate 20000 (DPC, Los Angeles) machine (reference range 5-12 µmol/L) using Immulate 2000 DPC kit and radioimmunoassay methods. Levels of vitamin B12 (reference range 200-900 pg/ml) and folic acid (3-17 ng/ml) were determined by the E170 modular system (Roche, Los Angeles) using Roche kit and chemiluminescenc immunoassay method.

Data was collected and recorded in forms. The statistical analysis was done using SPSS 16.0 for Windows. The comparison between the case and control groups was done using Mann-Whitney U test. Kruskal-Wallis variation was used for the comparison based on the diagnosis within the patient group. For statistically significant parameters Bonferroni modified Mann-Whitney U test was used. $p \leq 0.05$ was accepted as significant.

Results

The average age of the 100 participants (53 male and 47 female) was 64.3±5.2. 110 healthy volunteers were included into the control group. The average age of the patients in the control group was 49±7.2. 67% of them were male and 43% were females.

39 patients presented with chest pain, 32 with left lower extremity weakness, 9 with right lower and upper extremity weakness, 10 with dyspnea, 4 with confusion, 3 with syncope, 3 with unilateral leg swelling, 3 with extremity bruises, 2 with headache, 2 with imbalance, 1 with abdominal pain, and 1 with speech disruption.

The patients were diagnosed based on laboratory findings, imaging studies, and interventional methods. 42 of the patients were diagnosed with cerebral infarction (42%), 42 with acute myocardial infarction (42%), 8 with pulmonary embolism (8%), 3 with deep venous thrombosis (8%), 3 with peripheral artery embolism, 1 with sinus venous thrombosis, and 1 with portal venous thrombosis.

The mean homocysteine level in the patient group was significantly higher than that of the control group (p=0.02). Vitamin B12 level was significantly lower in the patient group (p=0.001). No statistically significant difference was noticed between the groups in terms of folic acid level (p=0.5) (Table 1).

Table 1. Demographical variable variables in two group

Group	Age (mean±SD)	Sex (male/female)
Control (n=110)	49±7.2	67/43
Case (n=100)	64.3±5.2	53/47

The mean vitamin B12 level in the ICE, portal venous thrombosis, NSTEMI, and STEMI patients was significantly lower than in the control group (p=0.04, 0.03, 0.025, and 0.001, respectively). No statistically significant difference was found between the serum B12 levels of DVT, PE, PAE and sinus venous thrombosis patients and the control group.

The mean serum folic acid levels in the acute PE, SVT, STEMI, and NSTEMI patients was found to be statistically lower than in the control group (p=0.001, 0.001, 0.001, 0.025, and 0.02, respectively). No significant difference was found between the ICE, DVT, and PVT groups and the control group in terms of mean folic acid level.

The mean plasma homocysteine level in the patients diagnosed with ICE, DVT, PE, SVT, STEMI, and NSTEMI was significantly higher than in the control group (p=0.001, 0.02, 0.001, 0.001, 0.001, and 0.001 respectively) (Table 2).

Discussion

Even though the mechanism of homocysteine is not well understood, it is thought to cause atherosclerosis due to endothelial cell injury. Homocysteine changes the endothelial anticoagulative effect and causes smooth muscle cell proliferation as a re-

Table 2. Control and case group, the mean plasma homocysteine in patients , serum vitamin B12 and folic acid levels and p-values

Group	ICD n=42	DVT n=3	APE n=8	SVT n=1	PAE n=3	PVT n=1	NSTEMİ n=32	STEMİ n=10	Control n=110
Serum B12 Level (pg/ml)	191±56	339±68	249±21	379±65	343±47	179±33	187±19	165±43	233±80
P Value	0.04*	0.12	0.057	0.37	0.17	0.03*	0.025*	0.00*	
Serum Folic Acid Level (ng/ml)	1.7±0.5	11±3.2	1.4±1	1.6±0.9	7.2±2.3	9±1.7	2.2±0.8	2±1.1	10.4±4
P Value	0.00*	0.32	0.000*	0.00*	0.23	0.15	0.025*	0.020*	
Plasma Hcy Level (µmol/L)	21.3±4.7	19±2.1	22±6.5	12±3.	7±2.7	6±3.9	23±7.2	24±2.6	7.7±3.4
P value	0.00*	0.025*	0.00*	0.078	0.15	0.17	0.00*	0.00*	

*p<0.05

Table 3. In the control group of patients , and vitamin B12, folic acid, and the average plasma homocysteine levels and p values compared to controls .

	B12 (mean±SD) (pg/ml)	Folic acid (mean±SD) (ng/ml)	Hcy (mean±SD) (µmol/L)
Control	233.6 ±80.7	10.49±4.06	7.77± 3.40
Case	520.6±400.8	13.48±7.50	11.81± 5.63
p Value	0.00*	0.5	0.02*

*p<0.05

sult of vascular endothelial injury [10, 11].

Studies have shown that increased plasma hcy levels are an independent factor for the development of coronary artery disease (CAD) [12-19]. Wilcken et al. were the first to mention the effect of abnormal hcy metabolism in CAD patients.

Iqbal et al.'s study of patients diagnosed with AMI showed that serum vitamin B12, B6, and folic acid levels in patients with a history of AMI and smoking were lower than those in non-smoking patients and than those of the healthy control group. On the other hand, plasma hcy levels were higher. This study suggested vitamin B12, B6, and folic acid replacement be considered in populations at risk to prevent the development of CAD [20].

Guo at al., in their study of unstable angina pectoris (UAP) patients, identified 22 cases with hyperhomocysteinemia (hhcy) and treated them with 5mg/day folic acid for 8 weeks. On the 4th and 8th weeks of treatment, endothelial functioning was measured using high-resolution B-mode ultrasonography of the brachial artery. On the 8th week of treatment, the hcy level in the hhcy group showed a significant decrease, but they reported that there was no significant correlation between the plasma hcy and serum folic acid levels and the improvement in the arterial endothelial functions [21].

In our study, patients presenting with AMI were divided into two groups, the STEMI and NSTEMI. Folic acid and vitamin B12 levels were significantly lower in both STEMI and NSTEMI groups compared to the control group. Hcy was also significantly higher in both groups compared to the control group. Moreover, changes in the serum vitamin B12, folic acid, and hcy levels were more prominent in these groups compared to the thromboembolic disease group. This result supports previous research. The hhyc and low serum levels of vitamin B12 and folic acid are important, and preventable, risk factors for CAD. The mean hcy levels of the STEMI, NSTEMI, and ICE groups were higher than in other thromboembolic patient groups. Mean hcy in the ICE group was 11±5.5 µmol/L; it was 14.0±5.5 µmol/L in the NSTEMI group and 12.3±9.7 µmol/L in the STEMI group. These results support the findings of the two studies mentioned above.

Cantu et al. published a study which assessed 45 patients with sinus vein thrombosis (SVT). A strong negative correlation was found between the high plasma hcy levels and low levels of folic acid. However, the same study could not show a similar correlation between the high plasma hcy and low serum vitamin B12 levels. In conclusion, this study reported that high plasma hcy and low serum folic acid levels are risk factors for SVT. Only 1 patient with SVT was included in our study. Like in the PE, STEMI, and NSTEMI groups, this patient's hcy level was higher than in the other thromboembolic disease groups. However, the number of SVT patients included in our study is insufficient to compare the vitamin B12, folic acid, and hcy levels with those of Cantu et al.'s [22].

Only a single patient with portal vein thrombosis (PVT) was included in our study. However, no significant difference was found between this patient's hcy level and that of the control group. No comments can be made due to the insufficient number of patients. Moreover, we could not find a similar study that enrolled a large number of PVT patients. Only a few case reports have been published. Buchel et al. reported a PVT patient with hhcy who had nodular regenerative hyperplasia and ischemic leg necrosis, i.e, generalized vasculopathy [23].

Case reports have presented cases of hhcy patients with pulmonary embolism (PE) [24, 25]. However, no studies were found to evaluate the hcy, vitamin B12 and folic acid levels in patients diagnosed with PE. Eight patients with PE were included in our study. These patients' mean plasma hcy level was significantly higher than that of the control group. The highest mean value was in the STEMI and NSTEMI patient groups. Mean folic acid levels were significantly lower compared to the control group, but vitamin B12 value was not significantly lower than that of the control group.

In our study, the mean plasma hcy levels of the ICE group was significantly higher than those of the control, PAE, and PVT groups. Even though mean serum vitamin B12 levels of the ICE group were significantly less than those of the control group, no similar difference was found in the folic acid group.

No patients with acute mesenteric ischemia were included in our study. One case control study of 63 patients with acute mesenteric vein thrombosis (AMVT) [26] reported that hhcy and low serum folic acid levels were risk factors for AMVT and that folic acid replacement reduced and prevented the recurrence of AMVT.

Studies on DVT patients [27, 28] reported that hcy was much higher in patients with lower extremity DVT, and they proposed that hhcy may play a role in developing DVT.

The mean plasma level of hcy of the DVT patients included in our study was significantly lower than those in the ICE, PE, STEMI, and NSTEMI groups, but it was significantly higher than that of the control group. Mean serum folic acid level of the DVT group did not show a significant difference from that of the control group, but the mean serum folic acid level of the

PE, STEMI, and NSTEMI groups were higher than that of the DVT group. No statistically significant difference in the mean serum vitamin B12 level was found between the DVT group and the other patient groups or the control group. These data show that hhcy is a risk factor in all thromboembolic diseases, and hcy is especially higher in those that carry a high mortality rate like ICE, PE, STEMI, and NSTEMI, which may be related to the higher mortality and poor prognoses of these diseases.

We could not find a study similar to ours, which had a control group and compared plasma hcy, serum vitamin B12, and serum folic acid levels in all thromboembolic diseases. However, Ho et al. published a paper comparing plasma hcy, serum vitamin B12, B6, and folic acid levels in patients with DVT (n=11), coronary artery disease (CAD) (n=33), and diabetes mellitus (DM) (n=20). In this study, the highest plasma hcy level was found in the CAD group followed by the DVT group; hhcy was reported as an important risk factor for CAD (29).

In our study, the lowest serum vitamin B12 level was in the NSTEMI group. It was followed by STEMI and ICE respectively. Serum folic acid levels were lowest in the PE group, followed by NSTEMI and STEMI respectively.

The most important limitation of our study is its short period and the low number of patients enrolled. Moreover, very few patients were found for some disease subgroups (sinus vein thrombosis, portal vein thrombosis, and peripheral artery embolism) because of the short period of the study. This limited our ability to compare these groups with the disease groups and with the control group.

As a conclusion, data provided by this study and other papers about this subject propose that hhcy, low serum vitamin B12, and folic acid levels are critical risk factors for thromboembolic incidences. Morbidity, mortality, diagnosis, and treatment costs are particularly high in AMI, embolic ICE, and PE. This increases the importance of hcy, vitamin B12, and folic acid levels as risk factors for these diseases. Necessary tests may be conducted on the patients who are at higher risk for thromboembolic disease (e.g. elderly 60 > years old) to determine their hcy, vitamin B12, and folic acid levels. Providing appropriate treatment for these metabolic imbalances may reduce the incidence, treatment costs, and morbidity and mortality in these patients. More comprehensive studies including larger number of patients with thromboembolic diseases may provide more detailed and clearer evidence about this subject.

Competing interests

The authors declare that they have no competing interests.

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